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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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(21) International Application Number: PCT/HU85/00040 (22) International Filing Date: 1 July 1985 (01.07.85) (31) Priority Application Number: 3616/83 (32) Priority Date: 2 July 1984 (02.07.84) (33) Priority Country: HU (71)(72) Applicant and Inventor: CSATÁRY, László [HU/HU]; Deres u. 7, H-1124 Budapest (HU). (74) Agent: PATENTBUREAU DANUBIA; Bajcsy-Zsilinszky ut 16, H-1368 Budapest (HU). (81) Designated States: AT (European patent), AU, BE (European patent), BR, CH (European patent), DE (European patent), DK, FI, FR (European patent), GB (European patent), IT (European patent), JP, LU (European patent), MC, NL (European patent), NO, RO, SE (European patent), SU, US.		Published <i>With international search report.</i>
(54) Title: AN ANTIVIRAL PREPARATION AND THE METHOD OF ITS PRODUCTION		
(57) Abstract A biological preparation for the treatment of virus infections, and the procedure of its production. The principle of the method is to combine attenuated Gumboro virus with at least one registered carrier. The preparation which is the object of the invention is characterized by comprising attenuated Gumboro virus.		

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AN ANTIVIRAL PREPARATION AND THE METHOD OF ITS PRODUCTION

Object

5 The object of the invention is a biological
preparation for the treatment of virus infections. Ob-
ject of the invention is also the procedure of its
production, and further objects are the use of attenuat-
ed Gumboro virus or Gumboro virus vaccine for treat-
10 ment of virus infections in humans, and the application
of these preparations to humans.

 The preparation is suitable for the treat-
ment of practically any virus infection, and is parti-
cularly efficient against Herpesvirus infections, neo-
15 plastic diseases, aphthostomatosis and collagen dis-
eases.

Professional information

 Hepatitis virus infection damages the liver
20 parenchyma. It has three different forms, known as epi-
demic hepatitis (hepatitis A virus infection), serum
hepatitis (hepatitis B virus infection) and non-A-non-
-B (or C) hepatitis, a condition presumably caused by
a hepatitis virus other than A or B.

25 The clinical course of the hepatitis A infec-
tion is relatively mild. Latency is usually 10-28 days.
The patient is confined to bed for 30-45 days, and
disability lasts still longer. The infection evokes
specific immunity to further hepatitis A infection(s).
30 but no vaccine is available for prevention.

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Hepatitis B infection takes a more serious clinical course, and its latency is also longer, 50 - 160 days. Virus B is much more resistant to thermic and chemical influences than virus A and most other viruses. Hepatocellular carcinoma is a frequent sequel to hepatitis B infection. This infection does not, as a rule, evoke an immune response. A vaccine prepared from the blood of convalescents is available against hepatitis B, but it has been little used on account of its possible side effects (AIDS) and high price.

As yet no preparation has been available for hepatitis therapy. The purpose of the present invention has therefore been to develop a biological preparation suitable for the therapy and control of viral hepatitis.

15

Disclosure of the invention

The object of the invention is the development, and method of production of an antiviral preparation containing attenuated Gumboro virus, with or without an adjuvant potentiating the latter's action.

Object of the invention is also the application of the above preparations, and the use of attenuated Gumboro virus, in human therapy.

The Gumboro virus vaccine is known and widely used in the veterinary field.

The Gumboro disease is an acute viral disease of chickens, affecting them mainly at the age of 3-6 weeks. Its main symptoms are watery diarrhea, hyper-

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trophy of the bursa of Fabricius, and inflammation of the lymphoid organs. In the USA the Gumboro disease, also known as infectious bursitis of chickens, was first described by Congreve in 1957. The disease also
5 occurs in European countries, among others in Hungary. The causal agent of the disease, an enterovirus, is noted for its high resistance. The symptoms set in abruptly after a latency of 2-4 days, and usually subside after a week; most losses occur between days 3 and
10 5 of the clinical course. In the outbreaks studied, morbidity was 1-30 %, and mortality was 4-5 %.

The Gumboro vaccine, i.e. the attenuated Gumboro virus used by us is prepared by methods known from the literature. For example, a freeze-dried vaccine
15 ne is prepared from attenuated virus propagated in primary or secondary fibroblast cultures from 10-11-day chick embryos. Sterile virus material of at least 10^6 TCID₅₀/0.1 ml titre may be used for production of the vaccine, as prescribed in the Pharm. Hung. VI. To the
20 sterile virus material is added 50 % skim milk, and 2 ml amounts of the vaccine are distributed to 10 ml vials for freeze-drying.

The expiration time of the vaccine is one year when stored in sealed vials at +4 °C. Safety testing
25 ing is performed in 15 SPF chickens aged 3 weeks; the birds must not show symptoms within 14 days of vaccination.

The freeze-dried vaccine is delivered in

packing units of 100, 200, 500 and 1000 doses, and is used for prevention of the Gumboro disease. It is administered orally, in the drinking water.

5 The vaccine described above is used as active substance of the preparation which is the object of the invention. Naturally the attenuated virus itself, or any solution (e.g. a physiological solution) thereof can also be used for that purpose.

10 The Gumboro virus is non-pathogenic for man even in its virulent state. Its attenuated form is doubly safe for humans.

Most human vaccines contain inactivated virus. However, the Gumboro vaccine - the object of the invention - is prepared exclusively from attenuated virus.
15 The underlying mechanism of its antiviral action is presumably an interference phenomenon, more precisely a competition between the infecting virus and the vaccine virus.

We observed that the action of the attenuated
20 Gumboro virus was potentiated mainly by certain tranquillizers. Of the latter the drugs of choice are the phenothiazine derivatives substituted usually in positions 2 and 10. Chlorpromazine (10-(3'-dimethyl-amino-propyl)-2-chloro-phenothiazine) proved to be the most
25 effective compound in this respect. The range of the possible potentiating agents is, naturally, not limited to phenothiazine-like tranquillizers.

Apart from chlorpromazine, promethazine,

methophenazine, aminopromazine and similar compounds can be used as potentiating agents.

The attenuated virus component of the preparation which is the object of the invention should preferably be adsorbed onto a common carrier substance.

A freeze-dried vaccine with carrier proved to be the most advantageous, but the preparation can also be delivered in other forms, such as solution, suppository, capsule, emulsion, suspension, etc.

The applied dose depends on the patient treated, actual composition of the preparation, stage of disease and virus strain used. Of the attenuated virus 1000 to 5000 U, preferably 3000 - 4000 U, should be used daily either in a single dose or in 2-5 divided doses. Administration on 6 consecutive days is usually sufficient for full effect. Application may be oral or rectal, but where local therapy is required, as in Herpesvirus infections, the preparation can be applied in the form of solution or ointment.

With a potentiating agent added, the dosage also depends on patient, stage of infection and type of causative agent. For example, chlorpromazine may be administered at the daily dose level of 10-15 mg. A synergistic preparation should contain 10-100 mg chlorpromazine for each 1000 U of attenuated virus.

The preparations which are the object of the invention have been tested in many animal experiments and human trials, and developed in these a practically

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100 % therapeutic effect against both hepatitis A and B, without any toxic side effect. They are suitable not only for symptomatic treatment, but also for prophylactic use: the contact persons of hepatitis A patients, 5 given Gumboro virus preventively within 5 weeks of latency, did not contract the infection.

Further animal experiments and clinical trials in virus infections other than hepatitis have revealed the therapeutic efficiency of the preparations 10 against many virus diseases.

The most promising results were obtained in the following conditions:

- Herpesvirus infections such as herpes simplex I, II, herpes zooster, cytomegalovirus disease, 15 infectious mononucleosis (Epstein-Barr virus);
- various viral neoplastic diseases, above all liver cancer;
- aphthostomatosis;
- collagen diseases, e.g. polyarteritis 20 nodosa.

Claims

1. Procedure for the production of a biological preparation against virus diseases, characterized by combination of attenuated Gumboro virus with at least one registered carrier.
2. Procedure according to claim 1, characterized by addition of a potentiating agent to the preparation.
3. Procedure according to claim 2, characterized by addition of chlorpromazine for potentiation.
4. Antiviral preparation characterized by comprising attenuated Gumboro virus.
5. Antiviral preparation according to Claim 4, characterized by comprising a registered carrier.
6. Preparation according to claim 4 and/or claim 5, characterized by comprising a potentiating agent.
7. Preparation according to claim 6, characterized by comprising chlorpromazine as potentiating agent.
8. Application of attenuated Gumboro virus or Gumboro virus vaccine for therapy of virus infections in humans.
9. Treatment of human virus infections with Gumboro vaccine or attenuated Gumboro virus.
10. Treatment of hepatitis with Gumboro

vaccine or attenuated Gumboro virus.

11. The treatment according to claims 9 and 10, characterized by using a potentiating agent.

INTERNATIONAL SEARCH REP RT

International Application No PCT/HU 85/00040

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) ⁴ According to International Patent Classification (IPC) or to both National Classification and IPC IPC ⁴ .: A 61 K 39/12, A 61 K 39/39																	
II. FIELDS SEARCHED <div style="text-align: right; font-size: small;">Minimum Documentation Searched ⁷</div> <table style="width: 100%; border-collapse: collapse;"> <tr> <th style="width: 30%; border-bottom: 1px solid black; font-size: small;">Classification System</th> <th style="border-bottom: 1px solid black; font-size: small;">Classification Symbols</th> </tr> <tr> <td style="padding: 5px;">Int.Cl⁴:</td> <td style="padding: 5px;">A 31 K 39/12, A 61 K 39/39</td> </tr> </table> <div style="text-align: center; font-size: x-small; margin-top: 5px;">Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched ⁸</div>			Classification System	Classification Symbols	Int.Cl ⁴ :	A 31 K 39/12, A 61 K 39/39											
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III. DOCUMENTS CONSIDERED TO BE RELEVANT ⁹ <table style="width: 100%; border-collapse: collapse;"> <tr> <th style="width: 10%; border-bottom: 1px solid black; font-size: small;">Category ⁹</th> <th style="width: 70%; border-bottom: 1px solid black; font-size: small;">Citation of Document, ¹¹ with indication, where appropriate, of the relevant passages ¹²</th> <th style="width: 20%; border-bottom: 1px solid black; font-size: small;">Relevant to Claim No. ¹³</th> </tr> <tr> <td style="text-align: center; vertical-align: top; padding: 5px;">X</td> <td style="padding: 5px;">DD, A, 143 793 (U. SCHMIDT, H. LIEBERMANN) September 10, 1980 (10.09.80), see claims 1-3, page 1, lines 5-21; page 2, line 33 - page 3, line 23, example <div style="text-align: center;">--</div></td> <td style="text-align: center; vertical-align: top; padding: 5px;">(1,4,5)</td> </tr> <tr> <td style="text-align: center; vertical-align: top; padding: 5px;">X</td> <td style="padding: 5px;">AT, B, 308 967 (BEHRINGWERKE AKTIENGESELL- (SCHAFT) July 25, 1973 (25.07.73), see claim 1; page 2, lines 10-13, 43-49; <div style="text-align: center;">--</div></td> <td style="text-align: center; vertical-align: top; padding: 5px;">(1,4,5)</td> </tr> <tr> <td style="text-align: center; vertical-align: top; padding: 5px;">A</td> <td style="padding: 5px;">US, A, 3 548 055 (J.M. MOULTHROP) December 15, 1970 (15.12.70), see claims 1,4; column 1, line 65 - column 2, line 35 <div style="text-align: center;">--</div></td> <td style="text-align: center; vertical-align: top; padding: 5px;">(1,4,5)</td> </tr> <tr> <td style="text-align: center; vertical-align: top; padding: 5px;">A</td> <td style="padding: 5px;">US, A, 3 885 011 (G. RENOUX, M. RENOUX) May 20, 1975 (20.05.75), see abstract; claims 7-9 <div style="text-align: center;">-----</div></td> <td style="text-align: center; vertical-align: top; padding: 5px;">(2,6)</td> </tr> </table>			Category ⁹	Citation of Document, ¹¹ with indication, where appropriate, of the relevant passages ¹²	Relevant to Claim No. ¹³	X	DD, A, 143 793 (U. SCHMIDT, H. LIEBERMANN) September 10, 1980 (10.09.80), see claims 1-3, page 1, lines 5-21; page 2, line 33 - page 3, line 23, example <div style="text-align: center;">--</div>	(1,4,5)	X	AT, B, 308 967 (BEHRINGWERKE AKTIENGESELL- (SCHAFT) July 25, 1973 (25.07.73), see claim 1; page 2, lines 10-13, 43-49; <div style="text-align: center;">--</div>	(1,4,5)	A	US, A, 3 548 055 (J.M. MOULTHROP) December 15, 1970 (15.12.70), see claims 1,4; column 1, line 65 - column 2, line 35 <div style="text-align: center;">--</div>	(1,4,5)	A	US, A, 3 885 011 (G. RENOUX, M. RENOUX) May 20, 1975 (20.05.75), see abstract; claims 7-9 <div style="text-align: center;">-----</div>	(2,6)
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⁹ Special categories of cited documents: ¹⁰ "A" document defining the general state of the art which is not considered to be of particular relevance "E" earlier document but published on or after the international filing date "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) "O" document referring to an oral disclosure, use, exhibition or other means "P" document published prior to the international filing date but later than the priority date claimed		"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art. "A" document member of the same patent family															
IV. CERTIFICATE <table style="width: 100%; border-collapse: collapse;"> <tr> <td style="width: 50%; padding: 5px;"> Date of the Actual Completion of the International Search 19 September 1985 (19.09.85) </td> <td style="width: 50%; padding: 5px;"> Date of Mailing of this International Search Report 24 September 1985 (24.09.85) </td> </tr> <tr> <td style="padding: 5px;"> International Searching Authority AUSTRIAN PATENT OFFICE </td> <td style="padding: 5px;"> Signature of Authorized Officer <div style="text-align: right;"><i>Trischler</i></div> </td> </tr> </table>			Date of the Actual Completion of the International Search 19 September 1985 (19.09.85)	Date of Mailing of this International Search Report 24 September 1985 (24.09.85)	International Searching Authority AUSTRIAN PATENT OFFICE	Signature of Authorized Officer <div style="text-align: right;"><i>Trischler</i></div>											
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FURTHER INFORMATION CONTINUED FROM THE SEC NO SHEET

V. ☐ OBSERVATIONS WHERE CERTAIN CLAIMS WERE FOUND UNSEARCHABLE

This international search report has not been established in respect of certain claims under Article 17(2) (a) for the following reasons:

1. ☒ Claim numbers 8-11 because they relate to subject matter not required to be searched by this Authority, namely:

Methods for treatment of the human or animal body by therapy -
see Article 17(2)a)i) and Rule 39.1, iv).

2. ☐ Claim numbers..... because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claim numbers..... because they are dependent claims and are not drafted in accordance with the second and third sentences of PCT Rule 6.4(a).

VI. ☐ OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING

This international Searching Authority found multiple inventions in this international application as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims of the international application.
2. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims of the international application for which fees were paid, specifically claims:
3. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claim numbers:
4. ☐ As all searchable claims could be searched without effort justifying an additional fee, the international Searching Authority did not invite payment of any additional fee.

Remark on Protest

- ☐ The additional search fees were accompanied by applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

Anhang zum internationalen Recherchenbericht über die internationale Patentanmeldung Nr.

Annex to the International Search Report on International Patent Application No. PCT/HU 85/00040

Annexe au rapport de recherche internationale relatif à la demande de brevet international n°.

In diesem Anhang sind die Mitglieder der Patentfamilien der im obengenannten internationalen Recherchenbericht angeführten Patentedokumente angegeben. Diese Angaben dienen nur zur Unterrichtung und erfolgen ohne Gewähr.

This Annex lists the patent family members relating to the patent documents cited in the above-mentioned International Search report. The Austrian Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

La présente annexe indique les membres de la famille de brevets relatifs aux documents de brevets cités dans le rapport de recherche internationale visé ci-dessus. Les renseignements fournis sont donnés à titre indicatif et n'engagent pas la responsabilité de l'Office autrichien des brevets.

Im Recherchenbericht angeführtes Patentdokument Patent document cited in search report Document de brevet cité dans le rapport de recherche	Datum der Veröffentlichung Publication date Date de publication	Mitglied(er) der Patentfamilie Patent family member(s) Membre(s) de la famille de brevets	Datum der Veröffentlichung Publication date Date de publication
DD-A- 143 793	10/09/80	None	
AT-B- 308 967	25/07/73	BE-A1- 772 448 CH-A - 560 760 DE-A -2 045 160 DE-B2-2 045 160 DE-C3-2 045 160 DK-B - 129 590 DK-C - 129 590 ES-A1- 394 860 FR-A5-2 106 482 FR-B1-2 106 482 GB-A -1 327 870 IL-A0- 37 682 IL-A1- 37 682 NL-A -7 112 237 NL-B - 150 684 US-A -3 769 400	10/03/72 15/04/75 30/03/72 22/08/74 10/04/75 28/10/74 24/03/75 01/01/75 05/05/72 18/10/74 22/08/73 29/11/71 30/06/74 14/03/72 15/09/76 30/10/73
US-A-3 548 055	15/12/70	None	
US-A-3 885 011	20/05/75	AU-A1-49 846/72 BE-A2- 793 530 CA-A1-1 007 567 DE-A1-2 263 094 FR-A1-2 230 345 FR-B1-2 230 345 IL-A0- 41 199 NL-A -7 217 768 ZA-A - 729 156	13/06/74 29/06/73 29/03/77 12/07/73 20/12/74 10/11/77 28/02/73 03/07/73 28/08/74